PATENT

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Applicant :	Vollmers, Peter, et al.	Art Unit :	1642
Serial No. :	10/506,763	Examiner :	Halvorson, Mark
Filed :	05/12/2005		
Title :	NEOPLASM SPECIFIC ANTIBODIES AND USES THEREOF		

Assistant Commissioner for Patents

Washington, DC 20231

DECLARATION UNDER 37 C.F.R. §1.132

Dear Sirs:

I, Dr. Heinz Peter Vollmers, do hereby declare and state that:

1. I am a resident of Würzburg, Germany. My residence address is: Bonhoefferstrasse 19, 97078, Würzburg, Germany. I received Diploma of Science degree in Biology from the University of Tübingen in Germany. I received a Doctor of Science degree in Biology from the University of Tübingen in Germany. I received a Doctor degree in Medicine from the University of Würzburg in Germany. I received a Professor degree in Medicine from the University of Würzburg in Germany.

2. I am one of the inventors of the subject matter described and claimed in United States Patent Application Serial No. 10/506,763, filed May 12, 2005, entitled: "NEOPLASM SPECIFIC ANTIBODIES AND USES THEREOF."

3. I am currently a professor at the University of Würzburg, Germany. My CV is attached which reflects my expertise in the fields of Immunology and Oncology. I am currently a consultant for Patrys Ltd, the assignee of the above-identified application.

4. I am familiar with the claims submitted in the accompanying Response and RCE.

5. It is my understanding that the claims submitted in the accompanying Response and RCE were informally considered by the Examiner in the course of an interview and were alleged to lack an adequate written description under 35 U.S.C. §112, first paragraph.

Antibodies and functional fragments that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:1 and a light chain variable region sequence at least 75% identical to SEQ ID NO:3

6. I submit this Declaration to affirm that one skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and functional fragments that specifically bind to at least one of the recited cell lines and (i) that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:1, and comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:3; (ii) that comprise a heavy chain variable region sequence at least 80% identical to SEQ ID NO:1, and comprise a light chain variable region sequence at least 80% identical to SEQ ID NO:3; (iii) that comprise a heavy chain variable region sequence at least 85% identical to SEQ ID NO:1, and comprise a light chain variable region sequence at least 85% identical to SEQ ID NO:3; (iv) that comprise a heavy chain variable region sequence at least 90% identical to SEQ ID NO:1, and comprise a light chain variable region sequence at least 90% identical to SEQ ID NO:3; or (v) that comprise a heavy chain variable region sequence at least 95% identical to SEQ ID NO:1, and comprise a light chain variable region sequence at least 95% identical to SEQ ID NO:3.

7. The following are objective facts, and conclusions based upon the objective facts, in support of this Declaration:

8. The specification discloses the heavy chain variable region amino acid sequence, SEQ ID NO:1, and the light chain variable region amino acid sequence, SEQ ID NO:3 (Figures 1 and 2). The specification discloses that heavy and light chain variable region sequences SEQ ID NOs:1 and 3 are derived from a human antibody (Example 2; see also, page 15, lines 23-28; and page 17, lines 7-13). The location of the CDRs in antibody variable region sequences is predictable using techniques known at the time of the invention (see, for example, Morea *et al.*, Methods 20:267 (2000)). A sequence alignment with a database of known human immunoglobulin sequences (e.g., IMGT, see the specification page 44, lines 9-20) can localize the CDRs. Thus, the skilled artisan would know the location of the three CDRs in heavy chain variable region sequence SEQ ID NO:1 and the location of the three CDRs in light chain variable region sequence SEQ ID NO:3. Furthermore, as the locations of the three CDRs in SEQ ID NOs:1 and 3 would be known to the skilled artisan and that SEQ ID NOs:1 and 3 are derived from a human antibody, the skilled artisan would also have known the location of the framework regions (FRs) in SEQ ID NOs:1 and 3, as well as the D- and J-regions in SEQ ID NOs:1 and 3. Consequently, the skilled artisan would know the majority of amino acid residues of SEQ ID NOs:1 and 3 that contribute to antigen binding.

9. The level of knowledge and skill in the art concerning antibody structure and function at the time of the invention was high. As evidence of the high level of knowledge and skill in the art, the specification discloses the function of antibody heavy and light chain variable and constant regions (page 17, line 25, to page 18, line 10; page 15, line 3). The

role of variable region sequences, including CDRs in antigen binding was well known to the skilled artisan at the time of the invention, as acknowledged in the Office Action (see, for example, pages 2-3 of the Office Action). Consequently, the level of knowledge and skill in the art concerning antibody structure and function at the time of the invention was high.

10. Because the amino acid residues of heavy and light chain variable region sequences SEQ ID NOs:1 and 3 that contribute to antigen binding would be known to one of skill in the art, and the level of knowledge and skill in the art concerning antibody structure and function was high, the skilled artisan would have known antibodies and functional fragments thereof with amino acid residues of SEQ ID NOs:1 and 3 that could be substituted (i.e., would likely not destroy binding activity), and therefore would envision heavy chain variable region sequences with 75% or more identity to SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and light chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.) that would have at least partial activity. To illustrate this point, an amino acid substitution, for example, a non-conservative or conservative substitution outside a CDR or FR region of SEQ ID NOs:1 or 3 would likely not destroy binding activity of an antibody. Conservative substitutions within a CDR or FR region of SEQ ID NOs:1 or 3 would also likely not destroy binding activity of an antibody. Thus, the skilled artisan would know with a high degree of confidence that an antibody comprising SEQ ID NO:1 or 3 with a non-conservative or conservative substitution located outside of a CDR or FR of SEQ ID NO:1 or 3, or a conservative substitution within a CDR or FR of SEQ ID NO:1 or 3, would very likely retain at least partial binding activity.

11. Typically, about half of the amino acid residues in a given heavy or light chain variable region sequence are not within one of the three CDRs. In view of the fact that there are a large number of amino acids outside of the CDRs, antibody variants that likely retain at least partial binding activity would be readily envisioned by the skilled artisan. Thus, the skilled artisan would also readily envision antibodies and functional fragments with heavy chain variable region sequences with 75% or more identity to SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and light chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.), that would retain at least partial binding activity without actually having to test the particular variant.

12. As stated above, the skilled artisan would, in view of the guidance in the specification and knowledge in the art, readily envision antibodies and functional fragments with heavy chain variable region sequences with 75% or more identity to SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and light chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.) that retain at least partial binding activity. The skilled artisan would also know that, by contrast, introducing a large number of non-conservative substitutions, insertions or deletions into the CDRs of SEQ ID NOs:1 or 3 would likely result in destroying binding activity. For example, the skilled artisan knows that heavy chain variable region CDR3 appears to be important to confer fine binding specificity (see, for example, Chen et al., J. Immunol. 147:2359 (1991)). Thus, the skilled artisan would also know that a large number of non-conservative substitutions, insertions or deletions of heavy chain variable region CDR3 would likely result in loss of antigen specificity. Consequently, the skilled artisan would also readily envision antibodies and functional fragments of SEQ ID NOs:1 and 3 with

sufficient substitutions, insertions or deletions such that the antibody or functional fragment would be unlikely to have binding activity.

13. The ability of the skilled artisan to envision antibodies and functional fragments with heavy chain variable region sequences with 75% or more identity to SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and light chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.), that would retain at least partial binding activity is further evidenced by the fact that humanizing antibodies was known to the skilled artisan at the time of the invention (see, for example, U.S. Patent No. 6,180,370). In particular, grafting non-human CDRs to human framework sequences and combining them with human constant region sequences was well established at the time of the invention. In view of the fact that all CDRs of a given variable region sequence could be transferred from one mammalian species to another without destroying binding activity of the resultant humanized antibody, the skilled artisan could clearly readily envision antibodies and functional fragments that comprise heavy chain variable region sequences with 75% or more identity to SEQ ID NO:1, and light chain variable region sequences with 75% or more identity to SEQ ID NO:3. Moreover, given that humanized antibodies retain binding, variable region sequences can include non-identical amino acids in many positions outside of the CDRs without destroying binding activity, and therefore can be substantially non-identical to SEQ ID NOs:1 and 3 outside of the CDRs. Consequently, the skilled artisan would readily envision a number of antibodies and functional fragments that vary in positions outside of the CDRs of SEQ ID NOs:1 and 3 that retain at least partial binding activity.

14. To corroborate that substitutions within CDRs can be tolerated, Kipriyanov et al. (Protein Engineering 10:445 (1997)) report that a substitution of a cysteine residue by a serine within CDR3 of any antibody heavy chain variable did not have an adverse effect on affinity. Thus, the skilled artisan would know antibodies and functional fragments with a substitution of a heavy or light chain variable region CDR residue can be tolerated and would not destroy binding activity.

15. To corroborate that substitutions within FRs can be tolerated, Holmes *et al.* (J. Immunol. 167:296 (2001)) report several heavy chain variable region FR substitutions of an anti-lysozyme antibody did not destroy binding activity. Thus, the skilled artisan would know antibodies and functional fragments with a substitution of a heavy or light chain variable region FR residue can be tolerated and would not destroy binding activity.

Antibodies and functional fragments that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:1 and a light chain variable region sequence at least 75% identical to SEQ ID NO:3, wherein the heavy or light chain variable region sequence has an insertion or deletion of one amino acid residue

16. I also submit this Declaration to affirm that one skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and functional fragments that specifically bind to at least one of the recited cell lines and that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:1 and a light chain variable region sequence at least 75% identical to SEQ ID NO:3,

wherein the heavy or light chain variable region sequence has an insertion or deletion of one amino acid residue.

17. The following are objective facts, and conclusions based upon the objective facts, in support of this Declaration:

18. As stated above, because the amino acid residues of heavy and light chain variable region sequences SEQ ID NOs:1 and 3 that contribute to antigen binding would be known to one of skill in the art, and the level of knowledge and skill in the art concerning antibody structure and function was high, the skilled artisan would have known antibodies and functional fragments thereof with amino acid residues of SEQ ID NOs:1 and 3 that could be substituted (i.e., would likely not destroy binding activity), and therefore would envision heavy chain variable region sequences with 75% or more identity to SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and light chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.) that would have at least partial activity. In addition, an amino acid insertion or deletion of SEQ ID NOs:1 or 3 would also likely not destroy binding activity of an antibody. Insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, occurs naturally during antibody affinity maturation (see, for example, Wilson *et al.*, J. Exp. Med. 187:59 (1998)). Thus, the skilled artisan would know with a high degree of confidence that an antibody comprising SEQ ID NO:1 or 3 with an amino acid insertion or deletion within or outside of a CDR, would very likely retain at least partial binding activity.

19. To further corroborate that antibodies and functional fragments with a heavy or light chain variable region sequence insertion or deletion can be tolerated, even within a CDR, Lantto and Ohlin (J. Biol. Chem. 277:45108 (2002)) report that single amino acid insertions or deletions of CDRs 1 and 2 of heavy chain variable region of an antibody were well tolerated. Thus, Wilson *et al.*, and Lantto and Ohlin corroborate that antibodies and functional fragments that comprise a heavy or light chain variable region sequence insertion or deletion even within a CDR can be tolerated.

20. In addition to the skilled artisan knowing antibodies and functional fragments that comprise heavy chain variable region sequences with 75% or more identity to SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and light chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.), and wherein the heavy or light chain variable region sequence has an insertion or deletion of one amino acid residue, such antibodies and functional fragments could be produced and binding activity verified in view of the guidance in the specification and knowledge in the art at the time of the invention. For example, producing recombinant proteins was routine in the art at the time of the invention, and the specification discloses routine assays for identifying antibodies that bind to the recited cell types, as well as cell proliferation/apoptosis assays. Methods of producing sequence variants including conservative amino acid substitutions at pre-determined locations are disclosed in the specification (page 22, line 17, to page 24, line 9). Methods of identifying antibody variants that have binding activity without undue experimentation were also known in the art and are also disclosed by the specification. In particular, methods for measuring antibody binding to the recited carcinoma cell lines, and methods for ascertaining cell

proliferation and apoptosis, are disclosed in the specification (page 44, example 3, to page 49 line 5). Additional methods for producing and screening antibodies for binding activity were known in the art at the time of the invention (see, for example, A Practical Guide to Monoclonal Antibodies by J. Eryl Liddell (Author), A. Cryer (Author), John Wiley & Sons, 1991). Thus, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention, one skilled in the art could readily produce antibodies and functional fragments that comprise heavy chain variable region sequences with 75% or more identity to SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and light chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.), and wherein the heavy or light chain variable region sequence has an insertion or deletion of one amino acid residue, that retain at least partial binding activity.

21. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 03/18/08

Heinz Peter Vollmers, Ph.D

Curriculum vitae

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Personal data

Date of birth	19. Februar 1952
Place of birth	21680 Stade, Niedersachsen, Germany
Citizen	deutsch
Family status	verheiratet
Kids	4

Education

1958-1963	Grundschule in Stade, Niedersachsen
1963-1965	Realschule in Stade
1965-1971	Humanistisches Gymnasium in Stade
1971-1973	Bundeswehrdienst
1973-1978	Biologiestudium an der Universität Tübingen
1978-1979	Diplomarbeit am Max-Planck-Institut für Biologie, Abt. Immungenetik
1979	Diplom in Biologie an der Universität Tübingen
1979-1981	Doktorarbeit am Max-Planck-Institut für Biologie, Abt. Immungenetik
1981	Promotion mit "magna cum laude" an der Universität Tübingen

Experience

1982-1985	Wiss. Ass. am Friedrich-Miescher Laboratorium der Max-Planck-Gesellschaft, Tübingen
1986	Akademischer Rat am Pathologischen Institut der Universität Würzburg
1991	Akademischer Oberrat am Pathologischen Institut der Universität Würzburg Habilitation für das Fach Experimentelle Pathologie Ernennung zum Privatdozenten (Dr. med)
1998	Professor f. Experimentelle Pathologie

Memberships Deutsche Krebsgesellschaft, Deutsche Gesellschaft für Immunologie, Deutsche Gesellschaft für Zellbiologie, Arbeitskreis Adhäsion, Metastasis Research Society (USA), New York Academy of Sciences, Planetary Society (USA),
American Association for Cancer Research AACR

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